Remarks

Claims 45-58 are pending in the subject application. The applicants acknowledge that claims 57-58 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, claims 57 and 58 have been canceled. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 45-56 are currently before the Examiner and favorable consideration of the pending claims is respectfully requested.

As an initial matter, the applicants note that the Office Action Summary page does not acknowledge the applicants' claim to foreign priority under 35 U.S.C. § 119 based on European application No. 03103580.1, filed September 26, 2003. The Notice of Acceptance of Application Under 35 USC 371 and 37 CFR 1.494 and 1.494 (Form PTO/DO/EO/903) indicates that the priority document has been received in the national stage file. The applicants respectfully request that their claim to foreign priority be acknowledged and made of record by the Examiner in the subject application.

In addition, the applicants note Figure 1 in the published U.S. application (US 2007/0141666A1) is not correct and does not correspond to the one published in international application PCT/EP2004/052302. Since the subject published application entered the national stage from international application PCT/EP2004/052302 after compliance with 35 U.S.C. 371, the applicants respectfully request the correct Figure 1 be substituted in the published application. For convenience, a copy of the correct Figure 1 from international application PCT/EP2004/052302 is attached.

Claims 45, 48, 49, and 53-56 are rejected under 35 U.S.C. § 102(b) as anticipated by Ashkenazi *et al.* (WO 99/53059). The applicants respectfully traverse the grounds for this rejection because the Ashkenazi *et al.* reference does not teach or suggest their claimed IgSP-tPA pre-propeptide.

The subject invention is directed to DNA constructs encoding an IgSP-tPA pre-propeptide. As recited in the claims and taught in the subject application at page 6, lines 4-12 (of the international published application), an IgSP-tPA pre-propeptide refers to a leader sequence that comprises an immunoglobulin signal peptide fused to a tissue-type plasminogen activator propeptide. A "leader sequence" is ***a sequence located at the amino terminal end of the precursor form of a***

protein and ***is cleaved during maturation***. The IgSP-tPA pre-propeptide of the invention is particularly advantageous in that it directs enhanced secretion and processing of proteins of interest (see, for example, page 5, lines 22-26).

Nowhere in the Ashkenazi *et al.* reference is there any teaching to fuse an immunoglobulin signal peptide (IgSP) with tPA to form an IgSP-tPA pre-propeptide (leader sequence). Rather, Ashkenazi *et al.* only teach the use of a tPA propeptide. For example, Ashkenazi *et al.* describe operably linking a mammalian tPA signal peptide, or fragments thereof (defined as a "precursor peptide" at page 6, lines 3-6), with a heterologous polypeptide of interest, where the tPA precursor peptide is capable of restoring the export and secretion of the heterologous polypeptide (see page 10, line 29 through page 11, line 24) and is cleaved during maturation (see, for example, page 6, lines 7-18 and page 11, lines 29-33). There is no description whatsoever by Ashkenazi *et al.* that their heterologous polypeptide encompasses immunoglobulin signal peptides (see, definition of "heterologous polypeptide" on page 6, line 28 through page 7, line 20). Moreover, the Ashkenazi *et al.* tPA precursor, pre-pro, or signal-pro peptide sequence (leader sequence) does ***not*** encompass the heterologous polypeptide (see page 10, line 29 through page 11, line 24, where the heterologous polypeptide is the protein of interest to be secreted and cannot be categorized as precursor, pre-pro, or signal-pro peptide sequences as defined at page 6, lines 3-18).

The Office Action at page 3 states "Ashkenazi *et al.* teach a construct comprising a human tissue plasminogen activator signal sequence fused to an IgG1 sequence (see figure 1 and brief description)." While generally accurate, this statement cannot logically be applied to the claimed invention, which is directed to an ***IgSP***-tPA ***pre-propeptide***. As noted above, a pre-propeptide refers to a leader sequence that is ultimately cleaved from the final protein product. A careful review of Ashkenazi *et al.* reveals the IgG1 sequence is actually an integral part of a chimeric protein of interest, TNFR1-IgG1, and is the fusion of the extracellular domain of the p55 TNF receptor to the hinge and Fc domain of an immunoglobulin heavy chain (see Brief Description of Figure 1 at page 6). As taught by Ashkenazi *et al.*, the secretion efficiency of TNFR1-IgG1 is increased as the result of operably linking its encoding sequence with that of a tPA precursor peptide encoding sequence, where ultimately only the tPA propeptide is cleaved from the secreted TNFR-IgG1 chimeric protein

(see, for example, Figure 1, page 8, lines 11-20, page 13, lines 5-12, and Example 5). Thus, Ashkenazi *et al.* cannot be said to have described each and every element of the claimed invention.

In another example, Ashkenazi *et al.* describe operably linking a tPA precursor peptide (SEQ ID NO:1) with a type 1 tumor necrosis factor receptor signal peptide (SEQ ID NO:2) to form a precursor peptide (see Office Action page 3). The skilled artisan would readily acknowledge that a type 1 TNFR signal peptide does not equate with an immunoglobulin signal peptide. Therefore, the applicants respectfully submit that no evidence has been provided that Ashkenazi *et al.* teach or even suggest each and every element of the claimed invention.

It is basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra; Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

In *Dewey v. Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

As noted above, the Ashkenazi *et al.* reference does not disclose a construct that encodes an immunoglobulin signal peptide fused to a tissue-type plasminogen activator propeptide to form an ***IgSP-tPA pre-propeptide*** Thus, under the applicable statutory and case law, the Ashkenazi *et al.*

reference does not anticipate the applicants' claims. Therefore, reconsideration and withdrawal of the rejection under 35 USC §102(b) is respectfully requested.

Claims 45, 48, 49, and 53-56 are rejected under 35 U.S.C. § 103(a) as obvious over Ashkenazi *et al.* (WO 99/53059) in view of Patel *et al.* (WO 00/52158). Applicants respectfully traverse the grounds for this rejection because the cited references, either alone or in combination, fail to teach or suggest the claimed invention.

Patel *et al.* disclose the use of a murine immunoglobulin (IgG) signal peptide for the recombinant expression of a protein, as shown in Fig. 15A and described in the application (see page 21, lines14-16 and page 43, lines 3-13). The Office Action contends at page 4 that the skilled artisan would have readily applied the known murine IgG sequence of Patel *et al.* to the polypeptides of Ashkenazi *et al.* to generate predictable results. The applicants respectfully disagree. The deficiencies of Ashkenazi *et al.* have been discussed above. Reiterating briefly, Ashkenazi *et al.* teach constructs encoding tPA and tPA fragments either alone or in combination with TNF1 signal peptides to form leader sequences or pre-propeptides. There is no teaching or suggestion whatsoever by Ashkenazi *et al.* to form a leader sequence (pre-propeptide) in which a tPA propeptide is fused with an immunoglobulin signal peptide. Patel *et al.* fail to correct the defects of Ashkenazi *et al.* Nowhere in Patel *et al.* is there a teaching or suggestion to combine its illustrated IgG signal peptide with a tPA propeptide.

All the claim limitations must be taught or suggested by the prior art in order to establish the *prima facie* obviousness of a claimed invention. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). As discussed above, there is no teaching or suggestion in either reference to a construct that forms a ***pre-propeptide*** in which an immunoglobulin signal peptide is fused with a tPA propeptide. Therefore, in the absence of these important features, the cited references, even combined, would not produce the claimed invention and a valid *prima facie* case for obviousness of the claimed invention has not been established by the Patent Office.

Even assuming, for the sake of argument, that *prima facie* obviousness has been established, the mere fact that the purported prior art could have been modified or applied in some manner to yield an applicant's invention does not make the modification or application obvious unless "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant.

KSR International Co. v. Teleflex Inc., 127 S. Ct. 1721 (2007). Furthermore, an assertion of obviousness without the required suggestion or expectation of success in the prior art is tantamount to using applicant's disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56CCPA 823, 160 USPQ 237, 243 (1969).

In the case of the presently claimed invention, it is unclear what motivation one of ordinary skill in the art would have had to apply the cited teachings and alter them to combine an immunoglobulin signal peptide with that of a tPA propeptide without the guidance and disclosure of the presently claimed invention. The applicants respectfully submit that the skilled artisan would not have envisioned that a leader sequence comprising an IgSP fused to tPA propeptide would have resulted in enhanced secretion of a recombinant polypeptide as demonstrated in the present application. Additionally, it is unclear what motivation exists to modify the teachings of Ashkenazi *et al.* with those of Patel *et al.* At best, one skilled in the art would have been motivated to substitute the signal and propeptide disclosed in Ashkenazi *et al.* with the murine IgSP sequence disclosed in Patel *et al.* since those elements could be considered equivalent to one another for directing protein secretion. However, no rationale has been provided or articulated in the Office Action explaining why one would add the IgSP disclosed in Patel *et al.* to the full construct disclosed in Ashkenazi *et al.* The applicants respectfully assert that any suggestion to create such a construct could only be arrived at through hindsight reconstruction which is improper. Therefore, the applicants respectfully request reconsideration and withdrawal of the obviousness rejection under 35 U.S.C. §103 based on Ashkenazi *et al.* as modified by Patel *et al.*

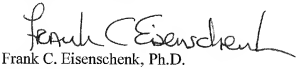
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. The applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/mhe/sl
Attachment: Correct Figure 1 from international application PCT/EP2004/052302